Acta Myologica • 2007; XXVI; p. 42-44

Glycogen storage disease type II: clinical overview

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Glycogen storage disease type II has a broad continuous clinical spectrum in terms of onset, involvement of organs and life expectancy.
Infantile onset is the most severe form, presenting with prominent cardiomyopathy, hypotonia, hepatomegaly and death before 12 months of life. Late onset form has onset at any age, lack of severe (or absence of) cardiac involvement, progressive skeletal muscle dysfunction and less dismal short-term prognosis.
In addition to muscle and heart involvement, other tissues are affected liver, spleen, endothelium, lung, brain, anterior horns, peripheral nerves.
In fact some patients with infantile form have hearing loss, abnormal brain myelination and central fever and some adult patients show aneurysms of brain arteries due to accumulation of glycogen in vessels.
As for other treatable lysosomal diseases, the advent of enzyme replacement therapy will change the natural history of this disease and also will increase our knowledge concerning clinical heterogeneity.

Key words: Alpha-galactosidase, cardiomyopathy, myopathy

Introduction

Pompe disease was first described in 1932 by the Dutch pathologist, JC Pompe, who observed glycogen storage within vacuoles in cardiac muscle and in other tissues of an 8-month-old girl who died from cardiac hypertrophy. Milder forms were described later and reported with other names including glycogen storage disease type II (GSD II), glycogenosis type II and acid maltase deficiency (AMD). Overall a common nomenclature is needed to improve the recognition of this disease in clinical practice; recently the name of Pompe disease has been proposed either for infantile onset form or for late onset forms.

Pompe disease is a lysosomal disease due to defect of acid alfa-glucosidase (GAA) deficiency. It is an extremely heterogeneous disease which varies regardless of age at onset, rate of disease progression and extent of organ involvement: symptoms may first occur in the first few months of life, but also may first appear in individuals in their sixties.

Classically it is classified in three forms (1):
- infantile form;
- childhood/juvenile form;
- adult form.

Infantile form ("classic" Pompe disease) presents with prominent cardiomegaly, hepatomegaly, weakness and and leads to death due to cardiorespiratory failure in the first year of life.

Some patients have an infantile variant form ("non-classic" infantile Pompe disease) with the onset within the first 6 months of age, less severe cardiomyopathy, predominance of muscular symptoms and survival beyond 2 years.

Childhood/juvenile form overlaps with non-classical infantile form; the clinical picture is characterized by proximal myopathy, absent or mild cardiac involvement and death before the end of the third decade of life.

Adult form overlaps with childhood/juvenile form, presenting with progressive proximal myopathy and usually without cardiac involvement.

However, this categorization remains challenging and ambiguous for many patients.

Recently 225 published cases of Pompe disease have been reviewed, showing a continous spectrum of phenotypes from non-classical infantile to adult disease. Therefore a new classification has been proposed (2):
- infantile form;
- late-onset form with onset at any age, less severe (or absent) cardiac involvement, progressive skeletal muscle dysfunction, less dismal short-term prognosis in comparison with infantile form.

Pompe disease prevalence appears to vary with ethnicity. Ausem, having analised 3 frequent GAA gene mutations associated with Pompe disease, calculated the prevalence of 1:138,000 births for infantile form and 1:57,000 births for late onset form and an overall prevalence of 1:40,000 births in the Dutch population (3, 4). Similar prevalence was found in a comparable study conducted in New York City (5). However in China population the prevalence of infantile form is estimated 1:50,000 and in Afro-Americans 1:31000 (1).

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Clinical Presentation

Infantile-onset Pompe disease

The clinical picture is dominated by cardiomyopathy, which is the consequence of glycogen storage in the heart. Cardiac hypertrophy begins in utero and becomes significant in the first few months of age. Massive cardiomegaly is evident in X-rays and Echocardiography provides evidence of increased thickness of the ventricular walls and interventricular septum, leading to obstruction of left-ventricular outflow.

Conduction abnormaties,due to interference of the glycogen storage with conducting tissues, produces tachyarrhythmia which can cause sudden death during infections, dehydratation, anesthesia.

The electrocardiogram typically shows short PR intervals and tall QRS complexes; true Wolf-Parkinson-White syndrome has been reported in some patients.

Progressive muscle weakness, manifested in a "floppy baby" appearence, and progressive respiratory insufficiency are the other key clinical features. Patients have also organomegaly (hepatomegaly, splenomegaly, macroglossia) and feeding difficulties.

By surveying 20 Dutch patients and 133 cases reported in literature, van den Hout documented that the median age at first symptoms ranged from 1.6 to 2.0 months and the median age at the death ranged from 6.0 to 8.7 months. Concerning the frequency of symptoms, cardiomegaly was present in all patients, hypotonia in 95% Dutch patients and 52% cases reported in the literature, feeding problems respectively in 55% and 44%, hepatomegaly in 90% and 29%, macroglossia in 45% and 29%, splenomegaly in 15% and 6% (6).

A retrospective multicenter study of 168 patients with symptom onset by 12 months of age demonstrated similar results: the median age at symptom onset was 2 months and at the death 8.7 months. Cardiomegaly (reported in 92% of patients), hypotonia (88%) cardiomyopathy (88%) respiratory distress (78%), muscle weakness (63%) were the most common findings (7).

Late-onset Pompe disease

The first symptoms are related or caused by muscle weakness, predominant in proximal lower limbs and paraspinal trunk muscles.

Secondary musculoskeletal impairements (contractures, deformities, lordosis, kyphoscoliosis, local pseudohypertrophy, osteoporosis) can occur. Consequently compromission of gross and fine motor function leads to use of wheelchair. Also articulation and phonation may be impaired as a consequence of oral-motor weakness.

Respiratory failure, which is due to diaphragmatic and respiratory accessory muscle involvement, often develops while patients are still ambulatory but it may even be the first clinical manifestation of the disease. Patients present with frequent respiratory infections, respiratory distress, orthopnea, sleep apnea, somnolence, morning headaches. As respiratory failure progress, assisted ventilation is required.

Cardiac disease among children ranges from unaffected to moderate cardiac hypertrophy and cardiac dysfunction while adult patients usually have no clinically identifiable heart disease.

A less frequent complication of late onset Pompe disease is vascular involvement of intracranial blood vessels; glycogen accumulation in vasculare smooth muscle, results in aneyeurysm and rupture of basilar artery, internal carotid artery and medial cerebral arteries (1).

In a review of 225 published cases of late onset Pompe disease the median age at the onset was 24 years (0-68), at the start of ventilation 34 years, at the start of wheelchair use 16 years, at the death 24.5 years.

Patients with a later onset of symptoms have a better prognosis (2).

Emerging clinical features

Natural history of infantile Pompe disease reflects the predominant involvement of cardiac and respiratory systems. However glycogen storage is autoptically present also in the brain, brainstem and anterior horns (8). It is expected that enzyme replacement therapy will have a tremendous beneficial impact upon systemic manifestations of Pompe disease, but enzyme does not cross blood brain barrier and cannot cure central nerve system disease.

Therefore neurological manifestations may be uncovered during long-term enzyme replacement therapy. The hearing loss was discovered in patients with infantile Pompe disease treated by enzyme replacement therapy. It was not reported before because the medical attention was drawn to the cardiopulmonary complications that lead to death in the first year of life. Hearing deficits are due to conductive apparatus and cochlea involvement and seem not to be present in patients with late onset form (9). Furthermore in some patients with infantile onset form delay myelination was shown by brain MRI (10). Finally some children experienced fever of central origin, causing death despite having had a good cardiac and muscular response to enzyme replacement therapy (11).

Diagnostic tests

In the first evaluation of a patient suspected of having Pompe disease laboratory testing should include serum creatine kinase, AST, ALT, LDH and tetrasaccharides in blood and urine. However, adult patients are reported to have normal creatine kinase (2). Due to variability of gly-

cogen accumulation between different muscles and muscle fiber types within muscle, lack of muscle glycogen storage demonstration does not exclude Pompe disease: actually 20% of late onset patients have a normal glycogen muscle content (2). GAA assay on skin fibroblasts or muscle biopsy is the diagnostic gold standard for diagnosis (12). White cells are unreliable tissue for measurement of enzyme activity because of interfering alternate isoenzyme activities: GAA assay in leukocyte can give false negative results in 10% of the patients (13), except for using inhibitors of interfering maltase, like acarbose. Dried blood spot assay by fluorometry or mass spectrometry is poised to become a reliable, non invasive and specific assay not only for diagnosis but also for possible newborn screening (14, 15). Residual enzyme activity is generally inversed correlated with disease severity, having infantile onset patients less than 1% of normal activity and late onset patients less than 40%; however patients with late onset and < 1% enzyme activity in skin fibroblasts are reported in the literature (12). Mutation analysis is used in the identification of heterozygotes when a familial mutation is known. Due to potential overlap of residual enzyme activity in late onset Pompe patients with heterozygotes, in some cases molecular analysis may be required to confirm diagnosis. Apart from the above case, mutation analysis may be helpful to diagnosis only in specific populations (for example R850X mutation in African Americans and D 645E in Chinese population).

For prenatal diagnosis molecular testing is the preferred method when both mutations are known; enzyme analysis in chorionic *villus* samples is preferred when molecular testing is not feasible or when enzyme analysis is an adjunct to molecular testing, though confirmation in amnyocytes may be considered if mutations are known (12).

Conclusion

With the advent of enzyme replacement treatment and other developing therapies, the recognition of Pompe disease in its variable clinical presentations has assumed a new importance.

As for other treatable lysosomal disorders a central database of patients will assist in obtaining a better understanding of the natural course of Pompe disease and in defining the standards of treatment.

References

1. Hirschorn R, Reuser AJJ. Glycogen storage disease type II: Acid alpha glucosidase (Acid maltase) deficiency. In: Scriver et al., eds. The Metabolic and Molecular bases of inherited disease. McGraw Hill; 2001. p. 3389-420.
2. Winkel LP, Hagemans MLC, van Doorn PA, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol 2005;252:875-84.
3. Ausem MGEM, Berg K, Kroos MA. Glycogen storage disease type II:birth prevalence agrees with predicted genotype frequency. Community Genet 1999;2:91-6.
4. Ausem MGEM, Vierbiest J, Hermans MMP. Frequency of glycogen storage disease type II in the Netherland. Implications for diagnosis and genetic counselling. Eur J Hum Genet 1999;7:713-6.
5. Martiniuk F, Chen A, Mack A. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with this disease. Am J Med Genet 1998;79:69-72.
6. Van den Hout HMP, Hop W, van Diggelen OP, et al. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from literature. Pediatrics 2003;113:332-40.
7. Kishnani PS, Hwu WL, Mandel H, et al. A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. J Pediatr 2006;148:671-6.
8. Raben N, Plotz P, Byme BJ. Acid alpha-glucosidase deficiency (glycogenosis type II, Pompe disease). Curr Mol Med 2002;2:145-66.
9. Kamphoven JHJ, de Ruiter NMM, Winkel LPF, et al. Hearing loss in infantile Pompe's disease and determination of underlying pathology in the knockout mouse. Neurobiol Dis 2004;16:14-20.
10. Chien YH, Lee NC, Peng SF, Hwu WL. Brain development in infantile-onset Pompe disease treated by enzyme replacement therapy. Pediatr Res 2006;60:349-52.
11. Van den Hout JMP, Kamphoven JHJ, Winkel LP, et al. Long-term intravenous treatment of Pompe disease with recombinant human alpha-glucosidase from milk. Pediatrics 2004;113:448-57.
12. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guidelines. Genet Med 2006;8:267-88.
13. Deyfus J, Poenaru L. White blood cells and the diagnosis of alpha glucosidase deficiency. Pediatr Res 1980;14:342-4.
14. Chamoles NA, Niizawa G, Blanco M, Gaggioli D, Casentini C. Glycogen storage disease type II: enzymatic screening in dried blood spot on filter paper. Clin Chim Acta 2004;347:97-102.
15. Zhang H, Kallwass H, Young S, Carr C. A comparison of methods for lysosomal acid alpha-glucsidase activity determination from dried blood spots for diagnosis of Pompe disease. Genet Med 2006;8:302-6.